CRH in the neonatal stress-response: Multiple regulatory levels

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The ability to respond to adverse environmental cues is present in an immature form in the neonatal and infant rat: stress-induced elevations of plasma corticosteroids during the first two postnatal weeks has been demonstrated by several groups, in cluding this lab. The limbic and hypothalamic mechanisms controlling the stress-response during this period are not fully understood, and are, therefore, the focus of this report.

Both hypothalamic corticotropin releasing hormone (CRH) and vasopressin (AVP) mediate ACTH release from the pituitary. The relative roles of these two peptides during the neonatal (first week) and infant (second week) developmental period, is controversial. Evidence from this lab is presented that argues strongly for a major role for CRH.

Up-regulation of hypothalamic CRH synthesis is a major component in the mature stress response. The developmental maturation of stress-induced enhancement of CRH-mRNA levels in the hypothalamic paraventricular nucleus (PVN) is discussed: By the ninth postnatal day, a "mature" up-regulation of CRH gene expression by cold stress is evident.

CRH-mediated neurotransmission, in both the endocrine and neuronal effector arms of the response to stress, may be modulated via alteration of receptor number. The first member of the CRH receptor family, CRF_1, has been demonstrated in brain, pituitary, and other organs, and probably mediates the neuroendocrine effects of CRH. CRF_1-mRNA distribution during development reveals several distinctive spatial and temporal patterns. In the hippocampal CA1, CA2 and CA3a, maximal (300-600% adult) CRF_1-mRNA levels are found on postnatal day 6. In the amygdala, CRH receptor mRNA levels peak on the ninth postnatal day (at 180% of adult values). In Cortex, a steady decline from high postnatal day 2 levels results in adult levels by day 12. These findings demonstrate distinct, regional, age-specific control of the synthesis of CRF_1. A second member of the CRH receptor family CRF_2, found mainly in the brain, has recently been defined. The developmental profile of CRF_2 mRNA may offer an additional control point for potential age-specific effects of CRH.

The developmental pattern of the expression of CRH receptors provide important information regarding modulation of age specific roles of CRH in different brain regions. For example, a high ratio of hippocampus/amygdala receptors may preferentially activate negative hippocampal input into the PVN during the neonatal period. Increased CRH receptor mRNA in the infant compared with the adult also provides a mechanism for the high excitatory effect of the peptide at this age.

In summary, there is increasing evidence for multiple control points for modulation of the early postnatal response and adaptation to stress. CRH secretion and synthesis in the hypothalamus and amygdala, and the abundance and distribution of at least two distinct CRH receptors in the limbic CNS and the pituitary may all be altered by environmental cues, permitting effective glucocorticoid secretion even during the "stress-hyporesponsive " developmental period.